(c) REMARKS

This application has been reviewed in light of the Office Action dated March 31, 2011. Claims 1, 2, 4, 11, 14, 25 and 26 are presented for examination, with claim 1 being in independent form. Claim 1 has been amended to further clarify and better define the intended invention. No new matter has been added. Favorable reconsideration is requested.

Initially, Applicants would respectfully like to draw the Examiner's attention to the fact that the European Patent Office (EPO) found the results set forth in the Declaration Under 37 C.F.R. § 1.132 of Stefan Van Der Geest (the "Declaration") to be compelling and issued an intent to grant the corresponding European application to the subject application, European Application No. 04758545.0, on April 11, 2011. Provided herewith as Attachment A is a copy of the Communication from the EPO stating the same, along with the allowed specification and claims. Applicants note that the European Examiner was applying prior art that differs from that of the U.S. Examiner, but respectfully submits that the significance of the Declaration's evidence is still highly relevant to the presently claimed invention.

Claims 1, 2, 4, 11, 14, 25 and 26 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,994,329 (Daifotis) in view of either U.S. Patent No. 4,817,819 (Kelly) or U.S. Patent No. 5,265,728 (Allendorf) and further in view of Palo Alto Medical Foundation, "Calcium and Nutrition PAMF Patient Health Information," January 2002 (Palo Alto Medical Foundation). Applicants respectfully traverse the rejections.

Prior to addressing the grounds of rejection, Applicants wish to briefly review certain features and advantages of the present invention. The invention is related to

a kit for promoting the proper sequential and continuous oral administration of a bisphosphonate and an accompanying nutrient over a 28 day period of time. The kit contains 4 unit doses of the bisphosphonate, wherein each dose is to be given once a week; 24 unit doses of a nutrient selected from the group consisting of calcium, calcium and vitamin D, and a combined unit dose of calcium and vitamin D to be given subsequent to the bisphosphonate administration and on the days between the days when each unit dose bisphosphonate is taken, and unit doses of calcium are about 400 mg to about 1500 mg of elemental calcium per day and unit doses of vitamin D are about 100 IU to 10,000 IU per day; and a blister card containing the unit doses, which are arranged in order of their use across the blister card. Further, the kit combines administration of an active with a calcium-containing nutrient, while providing a means wherein simultaneous dosing of the bisphosphonate and the calcium-containing nutrient is avoided. This combined administration increases the benefits achieved by the treatment since osteoporosis treatments are less effective in individuals with calcium and vitamin D deficiency. The subject kit also increases patient compliance and ease of administration.

Further, bisphosphonate and calcium should <u>not</u> be taken simultaneously because calcium interferes with absorption of the active (page 2, lines 28-38). To solve this problem, the kit of the present invention clearly teaches patients to take the accompanying calcium-containing nutrient on days only when not taking the active, thereby avoiding any problems associated with simultaneous dosing. *Id.* As such, the incorporation of a calcium-containing nutrient in the kit of the present invention is more than a memory aid, but serves a medical purpose to, in part, increase results of treatment with a bisphosphonate. This is a considerable advancement over the prior art.

The advantages and nonobviousness of the present invention is supported by the Declaration, which was submitted in this application on February 7, 2011. As explained therein, there is a problem in the field of osteoporosis treatment, wherein, despite the benefits of taking calcium and vitamin D in combination with bisphosphonate treatment to ensure sufficient availability of calcium for bone matrix mineralization, calcium homeostasis and avoidance of secondary hyperparathyroidism, only about 60% of bisphosphonate users currently take a calcium-containing supplement. In addition, 1 in 5 postmenopausal osteoporotic women take their calcium-containing nutrient and/or other medication incorrectly in relation to the bisphosphonate. It is a prevailing problem that patients often do not comply with the dosing instructions, and therefore, receive often significantly reduced benefit from the treatment. In fact, when a bisphosphonate is taken concurrently with a calcium product, the bisphosphonate is completely ineffective. Accordingly, correct administration of bisphosphonates is essential to successful treatment of osteoporosis.

The claimed invention addresses these needs and is specifically invented and designed to facilitate correct dosing to increase the likelihood that postmenopausal osteoporotic patients will receive both a calcium-containing nutrient and bisphosphonate, thereby providing better treatment to patients in need. The present invention does not contain a calcium-containing tablet on the day of the bisphosphonate intake but, for the rest of the week, it contains 6 (or 12) calcium-containing tablets. The kit of the present invention meets a need in the market and leads to significantly superior results in the treatment of osteoporosis in patients taking bisphosphonates.

Daifotis is directed toward a method for inhibiting bone resorption employing a bisphosphonate according to a continuous schedule. As acknowledged by the

Examiner, Daifotis fails to teach or suggest a blister pack as disclosed in the present invention. In addition, while Daifotis discloses the use of a bisphosphonate according to varying dosing schedules, it fails to specifically recite or suggest, by way of example, any regimens administering doses of a calcium-containing nutrient, and fails to teach or suggest the amount of calcium-containing nutrient that might be administered in unit doses in the kit. Daifotis lists possible additional dosages to the kit, including calcium, as a potential memory aid, however, it fails to specifically identify vitamins, or, more specifically, vitamin D.

At page 10 of the Office Action, the Examiner alleges that Daifotis discloses not taking calcium on the same day as the bisphosphonate. However, at column 13, lines 61-65, Daifotis generally states that placebo dosages, or calcium or dietary supplements, can be included to provide for a kit in which a dosage is taken every day. Accordingly, Daifotis does not teach that a calcium-containing nutrient should be taken in between the dosages of bisphosphonate for treatment and health benefits, as in the present invention. It would not be obvious to one reading Daifotis to choose a calcium-containing nutrient over the potentially hundreds of other options found within the recited "placebo dosages, or calcium or dietary supplements." Therefore, from Daifotis, one would simply not attain the medical benefits taught and achieved by the present invention.

Daifotis simply fails to teach or suggest the kit of the present invention, which contains calcium-containing nutrient for reasons other than as a memory aid, and fails to render obvious a kit containing bisphosphonate and a calcium-containing nutrient. Daifotis fails to appreciate the benefits achieved by the present invention as explained above and in the Declaration.

Kelly and Allendorf fail to remedy the deficiencies of Daifotis. Both Kelly and Allendorf are cited by the Examiner for teaching blister packs for storing and dispensing tablets. However, neither of the references teaches administration of unit doses of an accompanying calcium-containing nutrient. They merely teach that seven tablets in the blister pack might be a placebo or non-active tablet. As in Daifotis, the purpose of the blister packs is generally to act as memory aids. Further, there is clearly no disclosure or suggestion of the amount of calcium, or vitamin D to be administered in the unit doses as presently claimed, e.g., about 400 mg to about 1500 mg of elemental calcium per day and about 100 IU to 10,000 IU per day.

Palo Alto Medical Foundation fails to remedy the deficiencies of Daifotis, Kelly and Allendorf. This reference is cited by the Examiner for disclosing the recommended doses of calcium and vitamin D. However, the Examiner acknowledges that Palo Alto Medical Foundation fails to disclose a kit. It only teaches information on these supplements for patient health, including recommended daily doses. Therefore, Palo Alto Medical Foundation fails to specify a kit containing an active ingredient, and fails to offer any guidance on the dosing of the active in relation to the supplement and the benefits that may be achieved by a kit whereby simultaneous dosing is avoided.

Like Daifotis, Kelly, Allendorf and Palo Alto fail to teach or suggest the importance of correct dosing of a bisphosphonate and a calcium-containing nutrient, as fully explained in the Declaration, to avoid simultaneous daily dosing and gain the health and medical advantages achieved by using the kit of the present invention.

Accordingly, Applicants respectfully submit that Daifotis, Kelly, Allendorf and Palo Alto Medical Foundation, in any permissible combination, fail to render the present invention obvious and respectfully request withdrawal of the § 103 rejections.

In view of the foregoing amendments and remarks, favorable reconsideration and passage to issue is earnestly requested. Should the Examiner believe that issues remain outstanding, the Examiner is respectfully requested to contact Applicants' undersigned attorney in an effort to resolve such issues and advance the case to issue.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

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ATTACHMENT A

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15 APR 2011

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Application No.	Ref.	Date
04 758 545.0 - 1257	9192ML	11.04.2011
Applicant: Warner Chilcott Company, LLC		

Communication under Rule 71(3) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

Description, Pages

9-12	as published			
1-8, 13	received on	20-12-2010	with letter of	14-12-2010

Claims, Numbers

1-6+	received on	20-12-2010	with letter of	14-12-2010

Drawings, Sheets

1/4-4/4 as published

With the following amendments to the above-mentioned documents by the division

Description, Pages 2-8, 11, 12++

Comments

+ Article 84(EPC): claim 5 deleted and remaining claims renumbered. Claim 5 does not fall under the scope of claim 1.

++ Article 84 and Rule 42(1)(c) EPC: disclose invention as claimed.

A copy of the relevant documents is enclosed

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

You are requested within a non-extendable period of **four months** of notification of this communication

1. to file 1 set of translations of the claim(s) in the two other EPO official languages;

		EUR
2a. to pay the fee for grant including the fee for printing up to and including 35 pages;	Reference 007	830.00
2b. to pay the printing fee for the 36th and each subsequent page; number of pages: 0	Reference 008	0.00
3. to pay the additional claim fee(s) (R. 71(6) EPC); number of claims fees payable:	Reference 016	0.00
	Total amount	830.00

The mention of the grant of the patent shall be published in the European Patent Bulletin as soon as possible after the requirements concerning the translation of the claims and the payment of the fees for grant and printing, claims fees, designation fees and renewal fees as laid down in Rule 71(3), (4), (6) and (8) and (9) EPC are fulfilled.

If you do not approve the text intended for grant but wish to request amendments or corrections, the procedure described in Rule 71(4) EPC is to be followed.

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

If this communication is based upon an auxiliary request, and you reply within the time limit set that you maintain the main or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the enclosed claims contain amendments proposed by the Examining Division, and you reply within the time limit set that you cannot accept these amendments, refusal of the application under Article 97(2) EPC will result if agreement cannot be reached on the text for grant.

In all cases except those of the previous two paragraphs, if the fees for grant and printing or claims fees are not paid, or the translations are not filed, in due time, the European patent application will be deemed to be withdrawn (R. 71(7) EPC).

For all payments you are requested to use EPO Form 1010 or EPO Form 1010E or to refer to the relevant reference number.

After publication, the European patent specification can be downloaded free of charge from the EPO publication server https://data.epo.org/publication-server/ or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Upon request in writing each proprietor will receive the certificate for the European patent **together with one copy** of the patent specification provided that the request is filed within the time limit of Rule 71(3) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 71(3) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 71(3) EPC time limit, the certificate will be delivered without a copy of the patent specification (R.74 EPC, Decision of the President of the EPO, Special edition No.3, OJ EPO 2007, D.2).

Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and shall be in the language of the proceedings relating to the present application (cf. Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending and the time limit for filing divisional applications must be observed (Rule 36(1) EPC; Guidelines for Examination in the EPO, A-IV, 1.1.1).

Note on payment of renewal fees

If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (R. 71(9) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Filing of translations in the Contracting States

As regards translation requirements prescribed by the Contracting States under Article 65(1) EPC, please consult the website of the European Patent Office
www.epo.org →Patents →Law →Legal texts →National law relating to the EPC
www.epo.org →Patents →Law →Legal texts →London Agreement

In case of a valid extension

As regards translation requirements prescribed by the Extension States, please consult the website of the European Patent Office
www.epo.org →Patents →Law →Legal texts →National law relating to the EPC

Failure to supply a prescribed translation in a Contracting State or an Extension State may result in the patent being deemed to be void *ab initio* in the State concerned (Article 65(3) EPC).

Important note to users of the automatic debiting procedure

The fees for grant and printing and also any additional claims fees due under Rule 71(6) EPC will be debited automatically on the date of filing of the translation of the (relevant) claims, or on the last day of the period of this communication. However, if the designation fees become due as set out in Rule 71(8) EPC and/or a renewal fee becomes due as set out in Rule 71(9) EPC, these should be paid separately by another permitted means of payment in order not to delay the publication of the mention of grant. The same applies in these

circumstances to the payment of extension fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplement to OJ EPO 3/2009).

Important information concerning fee amounts
Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment**. The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epoline.org, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Payments by cheque delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

Examining Division:

Chairman:	Birlanga Pérez, J
2nd Examiner:	Schlaug, Martin
1st Examiner:	Ong, Hong Djien

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Enclosure(s): Form 2056
18 Copies of the relevant documents

Europäisches Patentamt
European Patent Office
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15 APR 2011

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Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 04 758 545.0

For the intended grant of the European patent, the bibliographical data are set out below, for information:

Title of invention:
- KIT ZUR PHARMAZEUTISCHEN VERWENDUNG
- KIT FOR PHARMACEUTICAL USE
- KIT UTILISABLE A DES FINS PHARMACEUTIQUES

Classification: INV. A61J1/03

Date of filing: 26.03.2004

Priority claimed: US / 26.03.2003 / USP457865

Contracting States* for which fees have been paid: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

Extension States* for which fees have been paid: AL LT LV MK

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*)	If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, **all Contracting States/Extension States** are currently still deemed to be designated. See also Rule 71(8) EPC and, if applicable, the above Note to users of the automatic debiting procedure.
**)	If two or more applicants have designated different Contracting States, this is indicated here.

~~KIT FOR PHARMACEUTICAL USE~~

FIELD OF THE INVENTION

The present invention relates to kits for the pharmaceutical administration of an ~~active~~ ingredient and one or more accompanying nutrients. These kits are particularly useful for treatment regimens wherein the ~~active ingredient~~ is administered on a continuous frequency other than daily and the nutrient is administered on the days in between the days the active ingredient is administered.

BACKGROUND OF THE INVENTION

With many treatment regimens, to achieve maximum efficiency of the active ingredients it is advisable to supplement the regimen with one or more nutrients. Therefore, the patient must remember not only to take the active ingredient, but also the associated nutrient. These dosages may require administration at different times of the day or under different conditions, for example, on an empty stomach vs. a full stomach. In addition, when the pharmaceutical active is not administered every day, remembering which day the active is to be taken can be confusing to the patient. Patient compliance with these types of programs is therefore an issue.

Many types of kits have been developed for dispensing pharmaceutical actives. Such kits include those designed to dispense active ingredients on a continuous daily frequency. See, e.g., U.S. Pat. No. 5,265,728, to Allendorf et al., issued Nov. 30, 1993; EP Pub. 0 511 726 A2, to Berlex Laboratories, Inc., published Nov. 4, 1992; PCT Pub. WO 99/51214, to Akzo Nobel, published Oct. 14, 1999; and U.S. Pat. No. 4,958,736, to Urheim, issued Sept. 25, 1990, which describe dispensers for administering various pharmaceuticals, including oral contraceptives, on a continuous daily basis, including regimens wherein the active ingredient is administered daily for about 21 days followed by placebo administration for about seven days. Other kits and dispensers have been developed that are designed for administering multiple doses of the same active ingredient per day, or for the concurrent or nonconcurrent administration of two or more active agents. See, e.g., U.S. Pat. No. 6,024,222, to Friberg et al., issued Feb. 15, 2000; U.S. Pat. No. 6,219,997, to Friberg et al., issued Apr. 24, 2001; U.S. Pat. Pub. 2003/0168376 A1, Taneja et al., published Sept. 11, 2003; U.S. Pat. Pub. 2003/0111479, Taneja et al., published June 19, 2003; U.S. Pat. No. 6,375,956, to Hermelin et al., issued Apr. 23, 2002; PCT Pub. WO 88/02342, Astra Läkemedel Aktiebolag, published Apr. 7, 1988; U.S. Pat. No. 4,295,567, to Knudsen, issued Oct. 20, 1981; DE 297 19 070, to Byk Gulden Lomberg Chemische Fabrik, published June 25, 1998; U.S. Pat. No. 5,848,976, to Weinstein, issued Dec. 15, 1998; U.S. Pat. No. 6,270,796, to

Weinstein, issued Aug. 7, 2001; U.S. Pat. No. 6,564,945, to Weinstein et al., issued May 20, 2003; and U.S. Pat. No. 5,788,974, to D'Amico et al., issued Aug. 4, 1998. A kit has also been disclosed for the administration of an active ingredient on a once weekly basis. See U.S. Pub. 2001/0044427, Mazel et al., published Nov. 22, 2001. However, none of these aforementioned kits or dispensers is designed or intended to address the compliance issues associated with the continuous administration of a pharmaceutical active on a frequency other than daily together with taking a separate associated nutrient on the days in between the days the active ingredient is administered.

Applicants have developed a dispensing means that addresses the issues presented. Applicants have found that the present invention simplifies complex therapies and aids patients in understanding how to take their medication and accompanying nutrients, which can then lead to greater compliance with complicated treatment regimens, for example, regimens wherein the patient takes a unit dose of an active ingredient on a continuous frequency other than daily and a unit dose of a nutrient on the days in between the days the patient takes the active dose.

The present invention is ~~particularly~~ useful in treatment regimens wherein the active ingredient is a bisphosphonate and the nutrient is calcium or a calcium-containing supplement. Patients taking bisphosphonates are generally instructed to take a daily calcium supplement, however, the bisphosphonate and the calcium supplement should not be taken at the same time. Because bisphosphonates chelate calcium, taking a unit dose of a bisphosphonate at the same time as a calcium supplement interferes with the absorption of the bisphosphonate, thereby potentially decreasing the efficacy of the bisphosphonate. The kit of the present invention addresses this issue. By taking the unit doses of nutrient on the days in between the days the patient takes the active dose, the patient avoids the problems associated with the simultaneous dosing of both a bisphosphonate and a calcium-containing supplement. Applicants have found that the present invention aids patients in understanding when and how to take bisphosphonates and calcium-containing supplements, which can lead to greater patient compliance and maximum benefit from such treatment regimens.

SUMMARY OF THE INVENTION

The present invention relates to a kit (i.e., article of manufacture) according to claim 1 for promoting the proper sequential oral administration of a ~~pharmaceutically active ingredient~~ bisphosphonate and accompanying nutrients, said kit comprising:

calcium-containing

bisphosphonate

(a) at least one unit dose of a ~~pharmaceutical active~~ to be given continuously on a frequency of once a week~~, twice a week, once every two weeks, twice a month, or once a month~~;

(b) at least one unit dose of a nutrient to be given subsequent to the active dose administration; and

(c) a blister card individually and releasably containing the unit doses;

bisphosphonate

wherein said unit doses of ~~pharmaceutical active~~ and nutrient are arranged horizontally or vertically in order of their use across the blister card.

calcium and vitamin D

~~Preferably~~, the pharmaceutical active is a bisphosphonate and the nutrient is calcium, ~~vitamin D~~, or a combined unit dose of calcium and vitamin D.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plan view of the front of a blister card.

FIG. 2 is a plan view of the back of the blister card of FIG. 1.

FIG. 3 is a plan view of the front of a blister card.

FIG. 4 is a plan view of the front of a blister card.

FIG. 5 is a plan view of the front of a blister card.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to ~~kits for the pharmaceutical administration of an active ingredient and accompanying nutrients. The kits are especially~~ useful in treatment regimens comprising the administration of a bisphosphonate once a week and calcium and/or vitamin D on the days in between the days the patient takes the bisphosphonate dose.

The terms "bisphosphonate" and "diphosphonate," as used herein, include acids, salts, esters, and derivatives thereof. The bisphosphonates of the present invention include those preferred compounds containing a nitrogen atom. Nonlimiting examples of bisphosphonates useful herein include the following: 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate) as described in U.S. Pat. No. 5,583,122, to Benedict et al., issued Dec. 10, 1996; 4-

< and on the days in between the days when the unit dose of the bisphosphonate is taken >

① bisphosphonate and calcium-containing

amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid or alendronate) as described in U.S. Pat. No. 4,621,077, to Rosini et al., issued Nov. 4, 1986; U.S. Pat. No. 4,922,007, to Kieczykowski et al., issued May 1, 1990; U.S. Pat. No. 5,019,651, to Kieczykowski, issued May 28, 1991; 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate); (4-chlorophenyl)thiomethane-1,1-diphosphonic acid (tiludronate) as described in U.S. Pat. No. 4,876,248 to Breliere et al., issued Oct. 24, 1989; 1.1-dichloromethylene-1,1-diphosphonic acid (clodronate) as described in Belgium Patent 672,205 (1966); cycloheptylaminomethylene-1,1-bisphosphonic acid (cimadronate), as described in U.S. Pat. No. 4,970,335, to Isomura et al., issued Nov. 13, 1990; 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate), which is described in U.S. Pat. No. 4,927,814, issued May 22, 1990; 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-bisphosphonic acid (zoledronate); and 1-(N-phenylaminothiocarbonyl)methane-1,1-bisphosphonic acid.

"Blister cards" are well known in the packaging industry and are widely used for packaging pharmaceutical unit doses. The blister cards of the present invention individually and releasably contain the unit doses of ~~pharmaceutical active and~~ <①> nutrient.

The terms "continuous" and "continuously," as used herein, mean at regular specified intervals. For example, a continuous frequency of once a week means that the active is given once a week for an unspecified period of time or for as long as treatment is necessary.

The term "once a week" or "once weekly" means that a unit dose is administered once a week, i.e., one time during a seven day period. ~~The term "twice a week" or "twice weekly"~~ means that a unit dose is administered twice a week, i.e., twice during a seven day period. In a twice weekly regimen, the unit doses may be administered on consecutive days during the seven day period, or may be administered about every three to four days. The term "every two weeks" means that a unit dose is administered once during a two week period, i.e., one time during a fourteen day period. The term "twice a month" or "twice monthly" means that a unit dose is administered twice, i.e., two times, during a monthly calendar period. In a twice monthly regimen, the unit doses may be administered on consecutive days, or may be administered once about every fourteen to sixteen days. The term "once a month" or "once monthly" means that a unit dose is administered once, ~~i.e., one time during a monthly calendar period.~~

The term "unit dose" or "unit dosage" means a dosage form containing an amount of ~~pharmaceutical active~~ bisphosphonate or nutrient suitable for administration in one single dose, according to calcium-containing

sound medical practice. The kits of the present invention are particularly useful for the administration of unit doses in the form of tablets and capsules.

The term "combined unit dose of calcium and vitamin D," as used herein, means a single unit dose form comprising both calcium and vitamin D.

The term "IU," as used herein, means International Units. One microgram of vitamin D is approximately 40 International Units.

The ~~frequency of administration of the pharmaceutical active depends on the treatment to be administered. A particularly preferred~~ treatment is the once weekly dosing of a bisphosphonate for the treatment of osteoporosis. The bisphosphonate is administered in an amount that has been determined to be therapeutically effective. For example, risedronate may be administered at a dose of 35mg per week. Alendronate may be administered at doses of 70 mg and/or 35 mg per week. Other treatment regimens for bisphosphonates may include those for cancer, Paget's disease, and other bone resorptive disorders.

The term "nutrient," as used herein, means any nutritional or dietary supplement including but not limited to vitamins, minerals, amino acids, herbs or other botanicals, or concentrates, metabolites, constituents, extracts, or combinations of the same.

The ~~preferred~~ nutrients to be administered in the bisphosphonate regimen are calcium, ~~and/or~~ vitamin D. Oral forms of calcium suitable for use in the present invention include capsules, compressed tablets, chewable tablets, and the like. Typical salt forms of calcium suitable for use in the present invention include but are not limited to calcium carbonate, calcium citrate, calcium malate, calcium citrate malate, calcium glubionate, calcium gluceptate, calcium gluconate, calcium lactate, dibasic calcium phosphate, and tribasic calcium phosphate. Different salt forms of calcium contain different percentages of elemental calcium. For example, calcium carbonate contains about 40% elemental calcium (i.e., 1000 mg calcium carbonate contains about 400 mg elemental calcium). In one embodiment of the invention, calcium can be administered at doses of 400 mg to 1500 mg of elemental calcium per day, on the days in between the days when the patient takes a unit dose of pharmaceutical active.

The term "vitamin D," as used herein, refers to any form of vitamin D that may be administered to a mammal as a nutrient. Vitamin D is metabolized in the body to provide what is often referred to as "activated" forms of vitamin D. The term "vitamin D" can include activated and non-activated forms of vitamin D, as well as precursors and metabolites of such forms.

(1) calcium and vitamin D, or a combined unit dose of calcium and

Precursors of these activated forms include vitamin D_2 (ergocalciferol, produced in plants) and vitamin D_3 (cholecalciferol, produced in skin and found in animal sources and used to fortify foods). Vitamins D_2 and D_3 have similar biological efficacy in humans. Non-activated metabolites of vitamins D_2 and D_3 include hydroxylated forms of vitamins D_2 and D_3. Activated vitamin D analogs cannot be administered in large doses on an intermittent schedule, due to their toxicity in mammals. However, non-activated vitamin D_2, vitamin D_3, and their metabolites may be administered in larger doses than "active" forms of vitamin D on an intermittent basis, without toxicity. ~~In one embodiment of the invention, vitamin D can be administered at doses of 100 IU to 10,000 IU of vitamin D per day, on the days in between the days when the patient takes a unit dose of pharmaceutical active.~~

In another embodiment of the invention, the nutrient is a unit dose comprising both calcium and vitamin D. In a further embodiment, the unit dose comprises 600 mg elemental calcium and 400 IU vitamin D, to be administered on the days in between the days when the patient takes the unit dose of the pharmaceutical active.

The kits of the present invention are ~~particularly~~ useful for administering ~~pharmaceutical actives such as~~ bisphosphonates on a weekly basis. The kits comprise at least one unit dose of a pharmaceutical active and at least one unit dose of a nutrient on a single blister card. In addition, the kits may include means for aiding the memory on the card. More than one week of dosage units may be present on one card and more than one card may be packaged together.

In one embodiment of the present invention, the blister card comprises a means for aiding the memory. Means for aiding the memory can include but are not limited to a listing of the days of the week, numbering, illustrations, arrows, Braille, calendar stickers, reminder cards, or other means specifically selected by the patient.

~~In one embodiment, the~~ The kit of the present invention provides a blister card comprising a unit dose of a pharmaceutical active suitable for once weekly dosing, and six unit doses of a nutrient, to be taken on the days in between the days the patient takes the weekly pharmaceutical active unit dose. In another embodiment of the invention, the blister card comprises a unit dose of a pharmaceutical active suitable for once weekly dosing and twelve unit doses of a nutrient, wherein two doses of nutrient are taken each day on the days in between the days the patient takes the weekly pharmaceutical active. ~~Preferably,~~ The pharmaceutical active is a bisphosphonate and the nutrient is calcium, ~~vitamin D~~ calcium and vitamin D, or a combined unit dose of calcium and vitamin D.

In a further embodiment of the present invention, the blister card comprises, in vertical arrangement in order of their use, a unit dose of a pharmaceutical active followed by six unit doses of a nutrient. In another embodiment of the invention, the blister card comprises, in vertical arrangement in order of their use, a unit dose of a pharmaceutical active suitable for once weekly dosing followed by twelve unit doses of a nutrient, wherein two doses of nutrient are taken each day on the days in between the days the patient takes the weekly pharmaceutical active. When two unit doses of nutrient are to be taken on the same day, the daily allotment of unit doses of nutrient can be arranged vertically or horizontally across the blister card. In a further embodiment of the invention, the kit can comprise at least two blister cards, wherein each blister card comprises doses suitable for one week of treatment therapy. In another embodiment, the kit can comprise at least four blister cards, wherein each blister card comprises doses suitable for one week of treatment therapy. In another embodiment of the invention, the blister card comprises two vertical columns of unit doses, wherein each vertical column comprises one unit dose of a pharmaceutical active and six or twelve unit doses of a nutrient. In a further embodiment of the invention, the blister card comprises four vertical columns of unit doses, wherein each vertical column comprises one unit dose of a pharmaceutical active and six or twelve unit doses of a nutrient. In yet another embodiment of the present invention, the blister card comprises two vertical columns of doses, wherein each column comprises unit doses sufficient for two weeks of therapy, arranged in order of their use (i.e., two vertical columns, each comprising a first unit dose of a pharmaceutical active, followed by six unit doses of a nutrient, followed by a second unit dose of a pharmaceutical active, followed by six more unit doses of a nutrient, for a total of fourteen unit doses per column). ~~Preferably,~~ the pharmaceutical active is a bisphosphonate and the nutrient is calcium, ~~vitamin D~~ calcium and vitamin D, or a combined unit dose of calcium and vitamin D.

In an alternate embodiment of the invention, the blister card comprises, in horizontal arrangement in order of their use, a unit dose of a pharmaceutical active followed by six unit doses of a nutrient. In another embodiment of the invention, the blister card comprises, in horizontal arrangement in order of their use, a unit dose of a pharmaceutical active suitable for once weekly dosing followed by twelve unit doses of a nutrient, wherein two doses of nutrient are taken each day on the days in between the days the patient takes the weekly pharmaceutical active. When two unit doses of nutrient are to be taken on the same day, the daily allotment of unit doses of nutrient can be arranged vertically or horizontally across the blister card. In a further embodiment of the invention, the kit can comprise at least two blister cards, wherein each blister card comprises doses suitable for one week of treatment therapy. In another embodiment,

the kit can comprise at least four blister cards, wherein each blister card comprises doses suitable for one week of treatment therapy. In another embodiment of the invention, the blister card comprises two horizontal rows of unit doses, wherein each horizontal row comprises one unit dose of a pharmaceutical active and six or twelve unit doses of a nutrient. In a further embodiment of the invention, the blister card comprises four horizontal rows of unit doses, wherein each horizontal row comprises one unit dose of a pharmaceutical active and six or twelve unit doses of a nutrient. In yet another embodiment of the present invention, the blister card comprises two horizontal rows of doses, wherein each row comprises unit doses sufficient for two weeks of therapy, arranged in order of their use (i.e., two horizontal rows, each comprising a first unit dose of a pharmaceutical active, followed by six unit doses of a nutrient, followed by a second unit dose of a pharmaceutical active, followed by six more unit doses of a nutrient, for a total of fourteen unit doses per row). Preferably the pharmaceutical active is a bisphosphonate and the nutrient is calcium, ~~vitamin D~~ calcium and vitamin D, or a combined unit dose of calcium and vitamin D.

The present invention provides a kit for providing complex therapeutic regimens to patients in a simplified manner, which can then lead to increased patient compliance. The figures exemplify an embodiment of the present invention.

Referring to FIG. 1, the blister card comprises cavities 10 in which the unit doses of the pharmaceutical active are contained. The general structure of these blister cards is well known in the art. These can comprise a clear or opaque film layer containing blister cavities 10 heat-sealed to a foil layer which includes indicia on one or both sides. The blister card further comprises cavities 11 in which the unit doses of nutrient are contained. It is appreciated that the individual blisters may vary in size and shape, depending on the size of shape of the unit dose of pharmaceutical active or nutrient releasably contained therein. As illustrated in FIG. 2, each blister card is printed with information to aid the patient in taking the doses. Such information includes the relative order of use in the treatments 30, the product name 31 and 33, and instructions as to when or how to take the dose 34.

The blister card of one embodiment of the present invention, presented in FIG. 1, contains one cavity 10 in which the unit dose of a pharmaceutical active is contained and six cavities 11 in which the unit doses of nutrient are contained to be taken on subsequent days for one week. The back of the blister card, FIG.2, provides memory aids 32 to reflect the appropriate information for proper dosing.

Referring to FIG. 3, another embodiment of the invention is shown wherein the blister card comprises four rows, each row containing one cavity 10 in which the unit dose of the pharmaceutical active is contained and six cavities 11 in which the unit doses of nutrient are contained. The patient takes one unit dose of a pharmaceutical active and then takes six unit doses of a nutrient on subsequent days, repeating this process four times.

Referring to FIG. 4, yet another embodiment of the invention is shown wherein the blister card comprises one cavity 10 in which the unit dose of the pharmaceutical active is contained and twelve cavities 11 in which the unit doses of nutrient are contained. The patient takes one unit dose of a pharmaceutical active and then takes two unit doses of a nutrient each day on subsequent days for one week.

Referring to FIG. 5, still another embodiment of the invention is shown wherein the blister card comprises two rows, each row containing a first cavity 10 in which a unit dose of pharmaceutical active is contained, followed by six cavities 11 in which unit doses of nutrient are contained, followed by a second cavity 10 in which a unit dose of pharmaceutical active is contained, followed by six more cavities 11 in which unit doses of nutrient are contained. In this embodiment, each row contains unit doses of pharmaceutical active and nutrient sufficient for two weeks of therapy when the pharmaceutical active is taken on a once weekly basis.

EXAMPLES

Example 1

A 75-year-old female patient diagnosed with osteoporosis is prescribed a weekly dose of 35 mg risedronate, in combination with calcium. The patient has difficulty remembering which day of the week she takes the risedronate dose, and occasionally forgets to take the calcium supplement, or takes the calcium supplement at the same time as she takes the risedronate weekly dose, thereby reducing the efficacy of the risedronate unit dose. The patient is presented with a blister card of the present invention, which contains in horizontal arrangement a unit dose of risedronate followed by six unit doses of 600 mg each elemental calcium. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient finds that this blister card is easy to use and aids her in remembering to take the risedronate on a weekly basis as well as the calcium supplement on the days in between the days she takes the risedronate doses. The patient also avoids taking a calcium supplement at the same time as she takes the risedronate unit dose, thus avoiding undesired

interaction between the two. The patient shows increased compliance with her prescribed treatment regimen.

Example 2

A 55-year-old female patient at risk for osteoporosis is prescribed a weekly dose of 35 mg risedronate in combination with a calcium and vitamin D supplement, as a preventative measure. The patient is presented with a blister card of the present invention, which contains four rows in horizontal arrangement, each row containing a unit dose of risedronate followed by six unit doses of a nutrient, each containing 600 mg elemental calcium and 400 IU vitamin D. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient uses this blister card for four weeks and finds that the package aids her in understanding her therapy and complying with her doctor's prescribed treatment regimen. The patient complies with instructions to take risedronate once a week and to take a supplement of calcium and vitamin D on the days in between the days she takes the risedronate doses, in accordance with her doctor's instructions.

Example 3

A 67-year-old female patient diagnosed with osteoporosis is prescribed a weekly dose of 70 mg alendronate, in combination with calcium. The patient has difficulty remembering which day of the week she takes the alendronate dose, and frequently forgets to take the calcium supplement. The patient is presented with a blister card of the present invention, which contains in vertical arrangement a unit dose of alendronate followed by six unit doses of 600 mg each elemental calcium. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient finds that this blister card is easy to use, and that it aids her in remembering to take the alendronate on a weekly basis as well as the calcium supplement on the days in between the days she takes the alendronate doses. The patient shows increased compliance with her prescribed treatment regimen.

Example 4

A 58-year-old female patient at risk for osteoporosis is prescribed a weekly dose of 35 mg alendronate in combination with a calcium and vitamin D supplement, as a preventative measure. The patient is presented with a blister card of the present invention, which contains four rows in vertical arrangement, each row containing a unit dose of alendronate followed by six unit doses of a nutrient, each containing 600 mg elemental calcium and 400 IU vitamin D. The blister card

contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient uses this blister card for four weeks and finds that the package aids her in understanding her therapy and complying with her doctor's prescribed treatment regimen. The patient complies with instructions to take alendronate once a week, and to take a supplement of calcium and vitamin D on the days in between the days she takes the alendronate doses.

~~Example 5~~

~~A 75-year-old male patient diagnosed with osteoporosis is prescribed a weekly dose of 35~~ mg risedronate, in combination with vitamin D. The patient has difficulty remembering which day of the week he takes the risedronate dose, and does not take a vitamin D supplement. The patient is then presented with a blister card of the present invention, which contains in horizontal arrangement a unit dose of risedronate followed by six unit doses, each containing 400 IU vitamin D. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient finds that this blister card is easy to use, and that it aids him in understanding his therapy and remembering to take the risedronate on a weekly basis as well as the vitamin D supplement on the days in between the days he takes the risedronate doses. ~~The patient shows increased compliance with his prescribed treatment regimen.~~

Example 5

A 72-year-old female patient diagnosed with osteoporosis is prescribed a weekly dose of 35 mg risedronate, in combination with 1200 mg elemental calcium daily, divided into two unit doses each day. The patient has difficulty remembering which day of the week she takes the risedronate dose, and occasionally forgets to take the calcium supplements. The patient is presented with a blister card of the present invention, which contains in horizontal arrangement a unit dose of risedronate followed by twelve unit doses of 600 mg each elemental calcium. The twelve unit doses of calcium are arranged in two rows following the unit dose of risedronate, as pictured in FIG. 4. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient finds that this blister card is easy to use and aids her in understanding her therapy and remembering to take the risedronate on a weekly basis as well as the calcium supplements on the days in between the days she takes the risedronate doses. The patient is able to understand her treatment regimen, and shows increased compliance therewith.

Example 6

A 65-year-old female patient diagnosed with osteoporosis is prescribed a weekly dose of 35 mg risedronate in combination with a calcium and vitamin D supplement. The patient is presented with a blister card of the present invention, which contains two rows of unit doses in horizontal arrangement, each row containing a unit dose of risedronate followed by six unit doses of a nutrient, followed by a second unit dose of risedronate, followed by six more unit doses of nutrient, as pictured in FIG. 5. Each unit dose of nutrient contains 600 mg elemental calcium and 400 IU vitamin D. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient uses this blister card for four weeks and finds that the package aids her in understanding her therapy and complying with her doctor's prescribed treatment regimen. The patient complies with instructions to take risedronate once a week and to take a supplement of calcium and vitamin D on the days in between the days she takes the risedronate doses, in accordance with her doctor's instructions.

Example 7

A 65-year-old female patient diagnosed with osteoporosis is currently taking risedronate on a weekly basis in combination with a calcium supplement. The patient is first shown a blister card of the present invention, which contains in vertical arrangement a unit dose of risedronate, followed by six unit doses of calcium. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient is then shown a second blister card having an alternate horizontal arrangement of unit doses, wherein the first row contains one unit dose of risedronate located in the center of the card, and the second row contains a horizontal arrangement of six unit doses of calcium. The second blister card also contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient prefers the first blister card over the second blister card. She determines that the arrangement of unit doses of the first blister card would aid her in remembering to take both the risedronate active and the calcium supplements on the correct days and in the correct manner. She also determines that the arrangement of the doses on the first blister card is clear and less confusing than the arrangement of the unit doses on the second blister card.

Example 8

A 70-year-old female patient diagnosed with osteoporosis is currently taking risedronate on a weekly basis in combination with a calcium supplement. The patient is first shown a blister

card of the present invention, which contains in horizontal arrangement a unit dose of risedronate, followed by six unit doses of calcium. The blister card contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient is then shown a second blister card having an alternate horizontal arrangement of unit doses, wherein the first row contains one unit dose of risedronate located at the left-hand side of the card, and the second row contains a horizontal arrangement of seven unit doses of calcium. The second blister card also contains printed information which instructs the patient as to how and in which order the doses are to be taken. The patient prefers the first blister card over the second blister card. She determines that the arrangement of unit doses of the first blister card would aid her in remembering to take both the risedronate active and the calcium supplements on the correct days and in the correct manner. She also determines that the arrangement of the doses on the first blister card is clear and less confusing than the arrangement of the unit doses on the second blister card.

All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

Claims

1. A kit for promoting the proper sequential oral administration of bisphosphonate and of accompanying nutrients on the days in between the days when the unit dose of the bisphosphonate is taken, said kit characterized by:

a) at least one unit dose of a bisphosphonate to be given continuously on a frequency of once a week;
b) at least one unit dose of a nutrient selected from calcium, calcium and vitamin D, and a combined unit dose of calcium and vitamin D to be given subsequent to the bisphosphonate administration and on the days in between the days when the unit dose of the bisphosphonate is taken; and
c) a blister card individually and releasably containing the unit doses;

wherein the blister card is characterized by one, two or four horizontal or vertical rows of unit doses, wherein each row is characterized by one unit dose of the bisphosphonate and six or twelve unit doses of the nutrient.

2. The kit of Claim 1 wherein the bisphosphonate is selected from the group consisting of risedronate, alendronate, pamidronate, tiludronate, cimadronate, ibandronate, and zoledronate.

3. The kit of Claim 1 wherein the kit is characterized by from two to four blister cards.

4. The kit of Claim 1 wherein the nutrient is calcium that is administered at doses of 400 mg to 1500 mg of elemental calcium per day, on the days in between the days when the unit dose of the bisphosphonate is taken.

~~5. The kit of Claim 1 wherein the nutrient is vitamin D that is administered at doses of 400 IU to~~ 10,000 IU of vitamin D per day, ~~on the days in between the days when the unit dose of the bisphosphonate is taken.~~

5. The kit of Claim 1 wherein the nutrient is a unit dose comprising both calcium and vitamin D, the unit dose comprising 600 mg elemental calcium and 400 IU vitamin D, to be administered on the days in between the days when the unit dose of the bisphosphonate is taken.

6. The kit of any of the Claims 1-5 for use in increasing compliance with a treatment regimen.

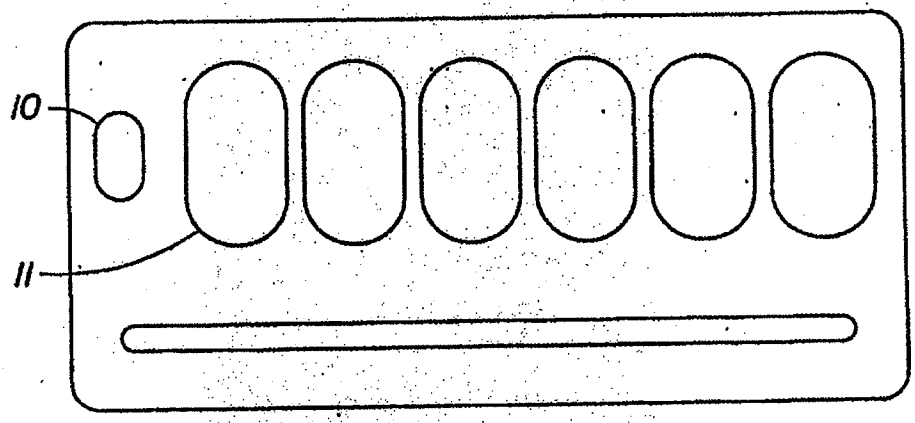

Fig. 1

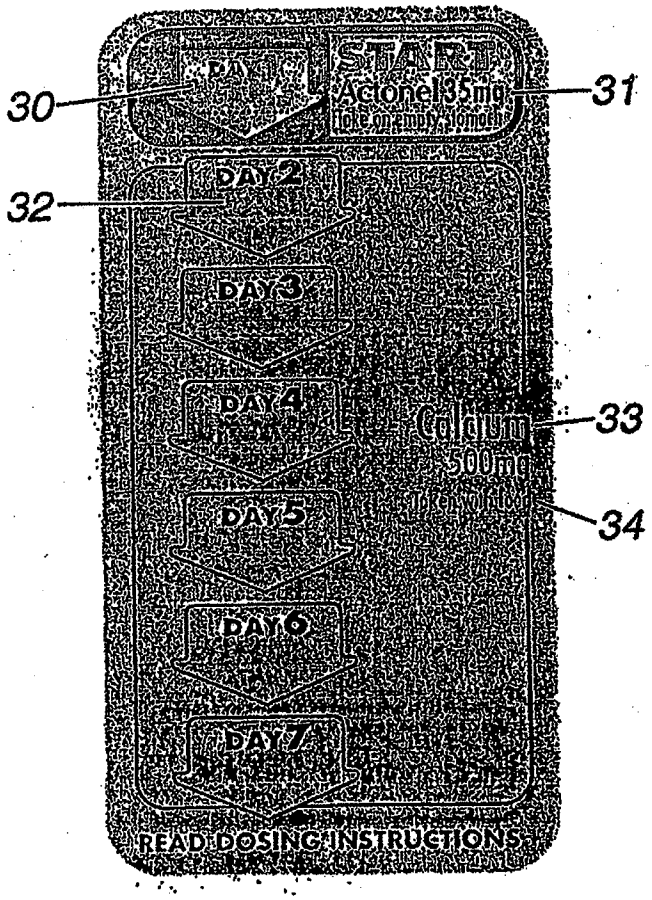
START
Actonel 35mg
DAY 2
DAY 3
DAY 4
DAY 5
DAY 6
DAY 7
Calcium
500mg
READ DOSING INSTRUCTIONS
30
31
32
33
34

Fig. 2

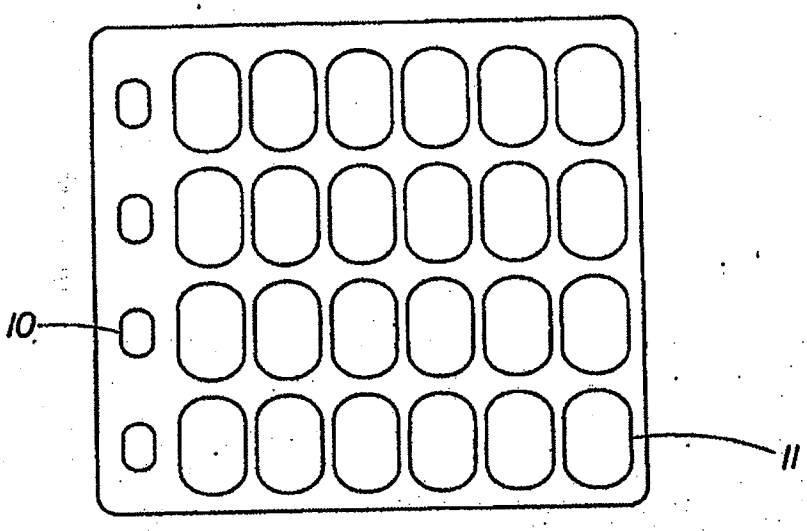

Fig. 3

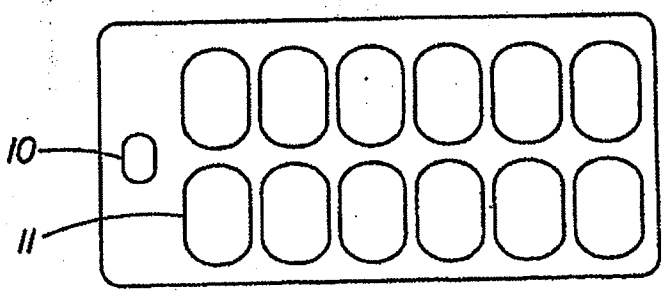

Fig. 4

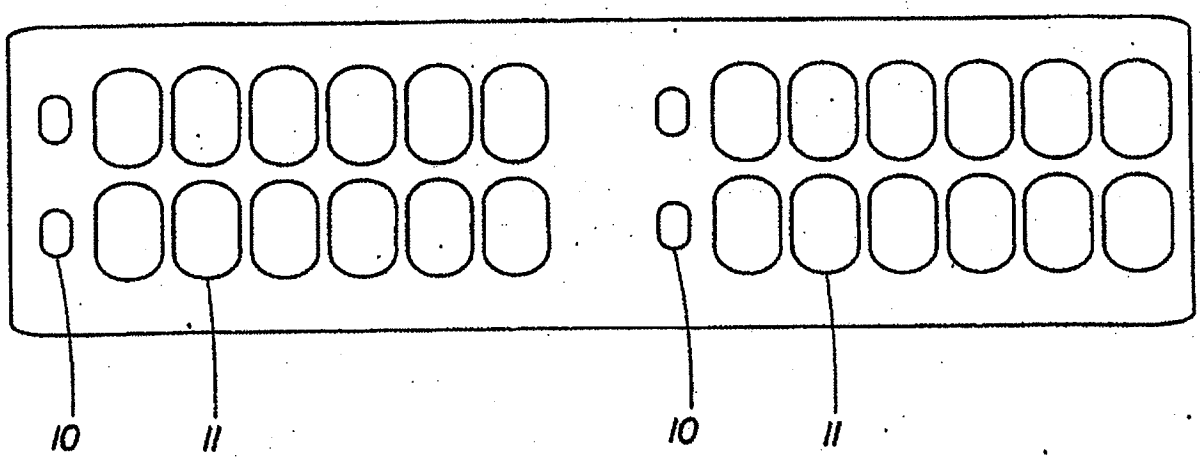

Fig. 5